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GRANT NUMBER DAMD17-96-1-6114

TITLE: Bone Density and Risk of Breast Cancer

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REPORT DATE: August 1997

TYPE OF REPORT: Annual

PREPARED FOR: Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 1997	Annual (1 Aug 96 - 31 Jul 97)

4. TITLE AND SUBTITLE
Bone Density and Risk of Breast Cancer

5. FUNDING NUMBERS
DAMD17-96-1-6114

6. AUTHOR(S)
Jane A. Cauley, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200*

The purpose of our study is to further evaluate the relationship between bone mineral density (BMD) and the risk of breast cancer among women age 65 years or older. All of the women are participants in the Study of Osteoporotic Fractures. We initially identified 121 cases of breast cancer over an approximate 3 years of follow-up. As part of the Department of Defense grant, we will extend the follow-up from 3 to 6 to 8 years. This extension will allow us to 1) verify our findings of a 2.5 fold increase in risk of breast cancer among women with the highest BMD compared to women with the lower BMD; 2) improve our power to look at the association between exogenous estrogen use, BMD, vertebral fractures and breast cancer; 3) improve our power to look at potentially important interactions including alcohol, estrogen, BMD and breast cancer and family history of breast cancer, BMD and breast cancer.

The scope of work involves 1) identifying potential breast cancer from the Year 6 (1992-1994) and Year 8 (1995-1997) examination of the cohort; 2) obtaining medical records; 3) adjudication of cases; 4) data analysis. The thrust of work during the first year of funding has been aimed at #1 through #3.

14. SUBJECT TERMS Breast Cancer, osteoporosis, estrogen

15. NUMBER OF PAGES
28

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

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Jane A Cauley 8/28/97

PI - Signature Date

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INTRODUCTION

The focus of the current application is furthering our understanding of the association between two of the most common conditions influencing a woman's health: osteoporosis and breast cancer.

We have recently reported that the relative risk of breast cancer increased with increasing BMD (1, and Appendix A). The risk of breast cancer among women in the top quartile of proximal radial BMD was 2.8 times higher than those in the lowest; the relative risks associated with top quartile BMD at the distal radius and calcaneus were 2.6 and 2.8, respectively. A test for linear trend was statistically significant for all BMD sites ($p < .01$). Results from Framingham have confirmed our findings (2). Incidence rates of breast cancer increased from 2.0 per 1000 person years among women in the lowest age specific quartile of metacarpal bone mass to 2.6, 2.7 and 7.0 among women in the second, third and highest quartile, respectively.

We have also found that among women not taking estrogen, those with vertebral fractures had 63% decreased risk of breast cancer (relative hazard=0.37; 95% confidence interval: 0.17 to 0.80; p=.01) than those not taking estrogen and this association remained significant after adjustment for potential confounding factors. These findings suggest that the use of estrogen therapy for women with vertebral fractures should be reexamined. However, these findings are based on a small number of cases. Extension of the follow-up will allow us to confirm these initial findings of exogenous estrogen and breast cancer among women with a vertebral fracture.

We have also investigated whether the level of breast cancer risk associated with BMD is different in women with a positive family history of breast cancer from than that in other women. Modification of the BMD effect of family history status was assessed by including interaction terms in logistic regression models. Relative to negative family history and lowest quartile proximal radius BMD, positive family history and highest quartile BMD together increased breast cancer risk 4.58-fold (95 percent CI (confidence interval) 1.88-11.14), whereas highest quartile BMD in the absence of a positive family history increased breast cancer risk only 1.75-fold (95 percent CI 0.84-3.65; p interaction=0.08). For the calcaneus, women with a positive family history and third quartile BMD appeared to be at highest risk. These results suggest that the association between BMD and breast cancer may be different in subgroups of women defined by family history.

We had complete family history data on 104 of the original 121 cases identified. There were only 20 cases of breast cancer among women with a positive family history. Hence, further follow-up of the cohort is needed to more fully understand whether the association between BMD and breast cancer differs in women defined by family history.

BACKGROUND

The metabolism of endogenous and exogenous estrogens is important in the etiology of breast cancer. The precise mechanism and risk relationships between estrogen and breast cancer remain controversial in spite of many years of both human and animal experimental research. There are several interesting hypotheses relating estrogen to breast cancer.

The production rate or blood levels of estrogen (especially free estradiol) may be directly related to the risk of breast cancer (5) as evidenced by the reduction in the rate of increase of breast cancer with age, by the benefits of both bilateral oophorectomy and the use of an anti-estrogen (Tamoxifen) in the survival of premenopausal breast cancer patients (6). The recently reported, fairly consistent relationship between obesity or weight gain pre- to postmenopause (7,8) and risk of breast cancer among postmenopausal women is consistent with the higher blood estradiol and estrone levels among heavier postmenopausal women (9). The relationship between endogenous estrogen levels and breast cancer is questionable because of the lack of, or a weak relationship between, exogenous estrogen therapy and risk for breast cancer even among women who have taken estrogen therapy for a relatively long time period (10). Selection criteria, especially for long-term estrogen therapy as well as differences in metabolism between oral estrogens and endogenous estrogens may explain (in part) the lack of excess risk associated with estrogen therapy.

In general, it is clear that steroid hormones are implicated in the risk of breast cancer although the precise underlying mechanisms remain undetermined (11). Population studies show estrogen exposure in the form of parity, age at menarche, and menopausal status to be linked to breast cancer risk. From experimental and clinical studies, it appears that estrogen can act directly on mammary tissue via estrogen receptors (12) and direct proliferative responses to physiologic doses of estrogen have been demonstrated (13).

Bone contains estrogen receptors (14) and is highly sensitive to estrogen levels in the body. Bone mineral density is positively correlated with early menarche and length of reproductive life (15). Oophorectomy (16) and prolonged amenorrhea (17,18) are associated with increased bone loss. Menopausal loss of ovarian estrogens in associated with rapid bone loss (19), eventually leading to an increased risk of fractures (20), both of which can be prevented by estrogen replacement therapy (21,22). Increased endogenous estrogen concentrations are related to increased BMD in both white and black elderly women (23,24).

If the strong relationship between bone mineral density is substantiated, then it is very likely that the association of exogenous hormone use and risk of breast cancer has been substantially underestimated because the selection of women for hormone replacement therapy would be inversely related to bone mineral density and risk of breast cancer.

BODY

Study Population

The study will utilize the women participating in the Study of Osteoporotic Fracture (SOF), a prospective study of risk factors for fracture among women aged 65+. The study originally included 9,704 women recruited in four communities: Baltimore, MD, Pittsburgh area (Monongahela Valley), Minneapolis, MN, and Portland, OR. The study began in 1986 and the current round of evaluations will be concluded in July, 1996. To be eligible to participate in SOF, the women had to be at least 65 years of age, living in the community, and able to walk without the assistance of other persons, and never had a bilateral hip replacement. The women represent community-living older individuals.

The women have now had five clinical evaluations (Table 1). In addition, women are contacted annually by questionnaire/interview. Breast cancer history was obtained at the first annual questionnaire (Year 1). Women who reported a history of breast cancer at Year 1 (approximately 500) were considered to have prevalent breast cancer and were not included in subsequent analysis of the evaluation of bone mineral density and breast cancer. The person-year at risk of incident breast cancer, therefore, begins after the Year 1 exam.

Table 1

Baseline 1986-1988 9,704 women	Risk factors Neuromuscular tests Functional status; Appendicular BMD 12cc serum: frozen storage X-4ays: spine, hip, hand
Year 2 Exam 1988-1990	Risk factors: update New neuromuscular performance tests Functional status; Hip and spine BMD 4cc serum: frozen storage
Year 3.5 Exam 1991 7,629	Repeat X-rays of spine Back pain, disability Functional status
Year 5.0 Exam 1992-1994	Fractional calcium absorption Neuromuscular and performance measures Hip and calcaneal BMD, ultrasound Risk factors Serum and urine: frozen storage
Year 8 Exam 1995-1996	Repeat pelvis X-rays Neuromuscular and performance measures Hip and calcaneal BMD Ultrasound of calcaneal and tibia Functional status

The study sample for the DOD proposal will be the 7,894 women of the 9,704 women included in the original analysis of the relationship of bone mineral density and breast cancer in SOF. Excluded from the prior analysis were: 1) 496 prevalent breast cancer cases at Year 1, 2) 3,650 women who died before the Year 3 exam and, therefore, could not be determined whether they had incident breast cancer (of which 5 had a diagnosis of breast cancer on the death certificates) and were not identified during the 3.5 year exam, 3) 618 who had no information regarding breast cancer at the 3.5 year exam, and 4) 160 with no information regarding breast cancer at Year 1 and, therefore, could not be classified as incident or prevalent. Breast cancer information was, therefore, collected on 8,561 (92% of the 9,339) women who survived to the 3.5 year exam and to be determined whether they had incident breast cancer. The 7,894 women without breast cancer at Year 3.5 exam will be the cohort for this study, and we will make a major effort to determine the incidence of breast cancer for all 7,894, including those who have died over the follow-up.

RESULTS/PROGRESS TO DATE

1. Acquisition of Estrogen Receptor/Progestin Receptor Status and TNM Staging

On our original cohort of 121 confirmed cases of breast cancer, we did not have information on receptor status or stage. We hypothesize that the association between BMD and breast cancer may differ by estrogen receptor status. To date we have collected ER/PR and TNM staging on 111 or 92% of the original 121 cases identified during the first 3 years of follow-up.

2. Identification of Breast Cancer from the Year 6 and 8 Exams (Visit 4 and 5).

We identified 165 potential breast cancer cases; 123 or 75% of these cases have been adjudicated locally. Once they have been adjudicated, they are sent to the Coordinating Center, the University of California at San Francisco for data entry. An expert pathologist reviews a sample of all of the cases and any case that has been identified as questionnable by the local physician adjudicator. Figure 1 shows the progress across the four clinics.

The event form that we developed is shown in Appendix B. Major problems we have identified is the difficulty in obtaining ER/PR test results. But, we have found that by contacting the Pathology department or the doctor's office directly, these difficulties are resolved.

RECOMMENDATIONS

None at the present time since we are still in the data collection phase.

CONCLUSIONS

The thrust of the first year is the complete adjudication of "all" breast cancers from the Year 6 and 8 examination. To date, we have adjudicated 75% of them. Clinics need to complete this task by 9/15/97. Data analysis will begin at that time.

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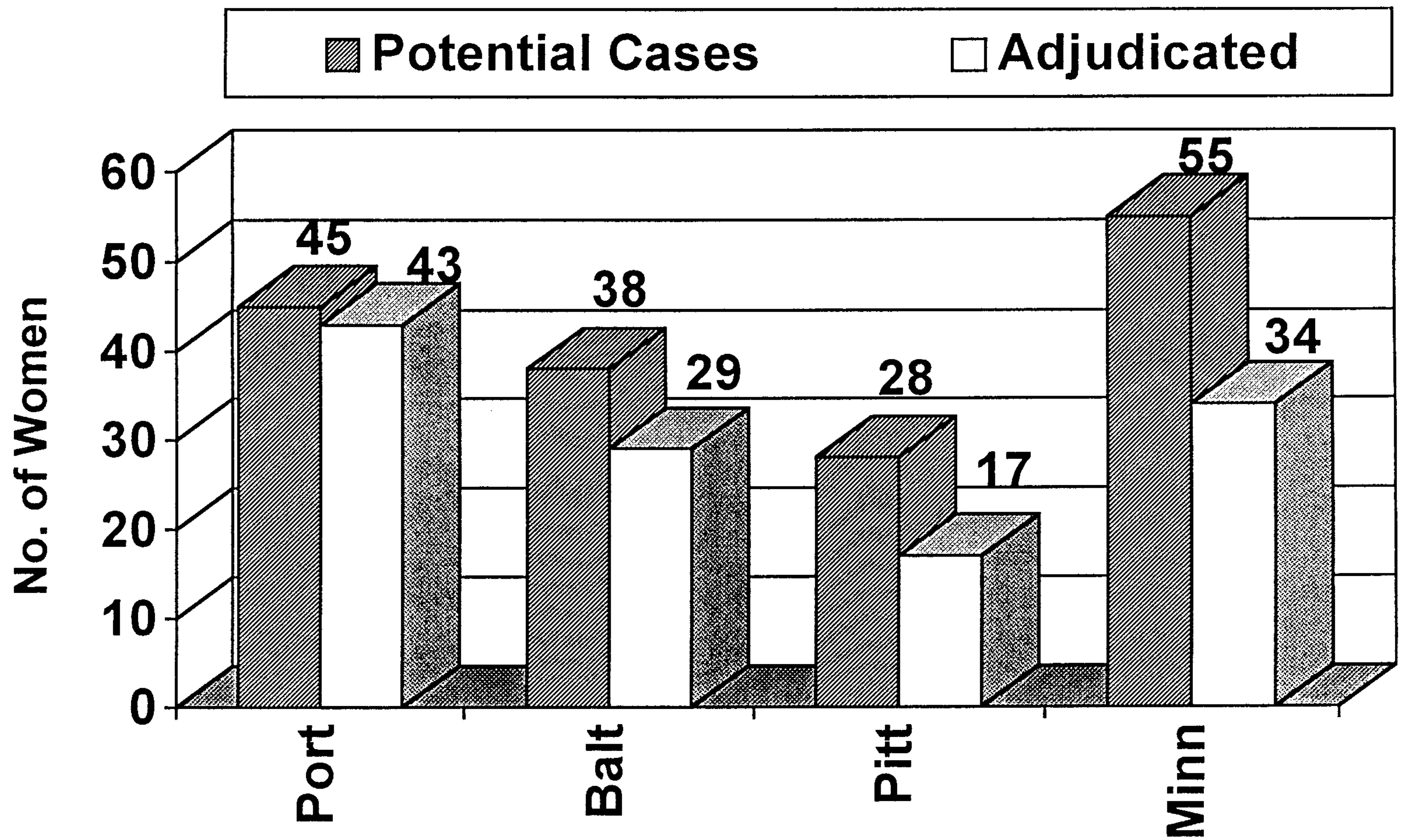
Progress in Ajudicating Potential Cases Identified at Visit 4 & 5 by Clinic



Appendix A

Bone Mineral Density and Risk of Breast Cancer in Older Women

The Study of Osteoporotic Fractures

Jane A. Cauley, DrPH; Frances Leslie Lucas, RN, PhD; Lewis H. Kuller, MD, DrPH; Molly T. Vogt, PhD; Warren S. Browner, MD, MPH; Steven R. Cummings, MD; for the Study of Osteoporotic Fractures Research Group

Objective.—To test the hypothesis that bone mineral density (BMD) is associated with the risk of developing breast cancer in older women.

Design.—Prospective cohort study with mean (SD) follow-up of 3.2 (1.6) years.

Setting.—Four clinical centers, one each located in the following areas: Baltimore, Md; Minneapolis, Minn; Portland, Ore; and the Monongahela Valley in Pennsylvania.

Participants.—A total of 6854 nonblack women who were 65 years of age or older and enrolled in the Study of Osteoporotic Fractures.

Measurements.—Radius and calcaneus BMD by single photon absorptiometry at baseline; hip and spine BMD by dual-energy x-ray absorptiometry 2 years later.

Main Outcome Measure.—Breast cancer confirmed by medical record review.

Results.—A total of 97 women developed breast cancer. In the multivariate model, adjusting for age, the degree of obesity, and other important covariates, the risk of breast cancer was about 30% to 50% higher per 1 SD increase in BMD (relative risk, distal radius BMD=1.50; 95% confidence interval, 1.16-1.95). The age-adjusted incidence rate of breast cancer per 1000 person-years among women in the lowest quartile of distal radius BMD was 2.46, compared with 5.99 among women with the highest BMD. Women with BMD above the 25th percentile were at 2.0 to 2.5 times increased risk of breast cancer compared with women below the 25th percentile. Results were consistent across all BMD sites.

Conclusions.—Bone mineral density predicts the risk of breast cancer in older women. The magnitude of the association is similar to that observed between BMD and all fractures. Our findings suggest a link between 2 of the most common conditions affecting a woman's health. Identifying a common denominator for these conditions should substantially improve our understanding of their etiology and prevention.

JAMA. 1996;276:1404-1408

From the Department of Epidemiology, Graduate School of Public Health (Drs Cauley, Lucas, Kuller, and Vogt), and the Department of Orthopedic Surgery, School of Medicine (Dr Vogt) University of Pittsburgh (Pa); Health Services Research, Maine Medical Center, Portland (Dr Lucas); Department of Biostatistics and Epidemiology (Drs Browner and Cummings), and Division of General Internal Medicine (Dr Cummings), University of California, San Francisco; and General Internal Medicine Section, Department of Medicine, Veterans Affairs Medical Center, San Francisco (Dr Browner).

A complete list of the Study of Osteoporotic Fractures Research Group appears at the end of this article.

Reprints: Jane A. Cauley, DrPH, University of Pittsburgh, Department of Epidemiology, 130 DeSoto St, Crabtree Hall A524, Pittsburgh, PA 15261.

A WOMAN'S lifetime exposure to ovarian hormones is dependent on a number of factors; most, if not all, of these factors are associated with the risk of breast cancer. Early age at menarche,[1,2] late age at menopause,[1,3] nulliparity,[3,4] and increased length of reproductive life[3,5] are all associated with an increased risk of breast cancer. Postmenopausal estrogens are associated with an increased risk of breast cancer in some,[6-8] but not all,[9,10] studies.

Prospective studies of the relation between endogenous estrogen concentrations and subsequent breast cancer have been inconsistent.[11-16] Interpretation of these studies is difficult since measurement of hormones at a discrete point in time may not reflect a woman's long-term exposure to estrogen. In addition, endogenous estrogens, specifically estradiol concentrations, are low in postmenopausal women; thus, there is a greater possibility of laboratory error.[17] Circulating estrogen levels in the blood may not relate to biological effects in tissue such as breast or bone.

See also pp 1389, 1397, and 1430.

Bone contains estrogen receptors[18] and is highly sensitive to circulating estrogen levels. Bone mineral density (BMD) is positively correlated with early menarche, length of reproductive life, and parity.[19] Oophorectomy[20] and prolonged amenorrhea[21] are associated with increased bone loss. Menopausal loss of ovarian estrogens is associated with rapid bone loss,[22] eventually leading to an increased risk of fractures,[23] both of which can be prevented by estrogen replacement therapy.[24,25] Increased endogenous estrogen concentrations are related to increased BMD in elderly women.[26]

If an older woman's BMD is a useful marker of her exposure to estrogen, then higher levels of BMD should be associated with an increased risk of breast cancer. To test the hypothesis, we analyzed data from the Study of Osteoporotic Fractures, a prospective multicenter study of a cohort of women aged 65 years or older. We measured BMD at baseline, ascertained information about breast cancer at year 1, and had a mean of 3.2 years of follow-up for the incidence of breast cancer.

METHODS

Subjects

A total of 9704 women aged 65 years or older were recruited between 1986 and 1988 from a center located in 1 of the following 4 areas: Baltimore, Md, Minneapolis, Minn, the Monongahela Valley in Pennsylvania, and Portland, Ore. The Study of Osteoporotic Fractures excluded black women because of their low risk of hip fracture, those unable to walk without the assistance of another person, and women with bilateral hip replacements.[27] One year after the baseline examination, women were asked to complete a follow-up questionnaire that included information about personal and family history of breast cancer. Follow-up information on breast cancer was collected a mean of 3.2 years later (range, 1.0-6.6 years). The institutional review boards at each institution approved the study. All participants signed an informed consent at entry into the study and at each clinical examination.

Ascertainment of Breast Cancer

For this breast cancer analysis, we included only women who provided information on breast cancer status at both year 1 and a mean of 3.2 years later (Table 1). A total of 365 women died before completing the follow-up information on breast cancer: 100 women before year 1 and 265 women between year 1 and the end of follow-up. Of these 265 women, 19 had breast cancer listed as cause of death. Of the 19 women who died, 17 reported prevalent breast cancer at year 1, 1 denied breast cancer at year 1, and information was missing for 1. Women who reported a history of breast cancer at year 1 were considered prevalent cases and excluded from further analysis (n=506). We confirmed 121 breast cancer cases, including 4 cases of carcinoma in situ, by review of the medical record by a physician epidemiologist (L.H.K.). Thus, we collected data about breast cancer from 8545 (91%) of the 9339 women who survived to the follow-up examination. Because use of estrogen replacement therapy could confound the association between BMD and breast cancer, we excluded women reporting current estrogen replacement therapy at baseline, leaving 97 confirmed breast cancer cases and 6757 controls.

Measurement of Bone Mass

Bone mass at entry into the study was measured in grams per square centimeter, using OsteoAnalyzers (Siemens-Osteon, Wahiwa, Hawaii). We scanned the distal and mid radius and the calcaneus with mean coefficients of variation of 1.5% for the distal radius, 2.0% for the mid radius, and 1.3% for the calcaneus.[27] During a second examination of the cohort (1988-1990), measurements of the BMD of the proximal femur and lumbar spine (L-1 to L-4) were made using dual-energy x-ray absorptiometry (QDR 1000, Hologic Inc, Waltham, Mass) with mean coefficients of variation of 1.2% for the femoral neck and 1.5% for the lumbar spine.[28]

Other Variables

Weight (in light clothes with shoes removed) was recorded with a balance beam scale.[29] Self-reported height at age 25 years was used to calculate the body mass index (BMI; weight in kilograms divided by the square of height in meters) because women with low bone mass experience height loss secondary to vertebral fractures. A reproductive history was obtained by questionnaire and interview, including information on age at menarche, first birth, and menopause, parity, type of menopause, history of benign breast disease, family history of breast cancer, and history of osteoporosis or spine fracture. Participants were asked about current and past use of estrogen since age 40 years and progestin (by pill, patch, or injection). Reports of current medications were checked against the labels of drugs brought to the clinic visit. We collected information regarding current and lifetime cigarette and alcohol use. The measure of alcohol use was drinks per week adjusted for atypical drinking, especially heavy drinking in the past 30 days. Women were asked whether they walked for exercise. A modified Paffenbarger questionnaire was administered to assess sports and leisure time activity expressed in kilojoules per week, averaged over the past year. The average number of blocks walked per day was also recorded.

Statistical Analysis

Descriptive characteristics of cases and controls were compared by *t* test for continuous variables and χ^2 for categorical variables. Proportional hazards regression models were used to assess the relationship between BMD and breast cancer. Bone mineral density was entered as a continuous variable to estimate the relative risk (RR) of breast cancer per 1 SD increase in BMD. Also, BMD was divided into quartiles based on the distribution of the cohort as a whole. Age-adjusted incidence rates were calculated for each quartile. The RR of breast cancer was estimated by quartile of BMD, using the lowest quartile as the reference group. We initially adjusted for age, modified BMI (weight divided by the square of height at 25 years of age), and family history of breast cancer. Because inclusion of cases with carcinoma in situ is controversial, we excluded those cases (n=4) in a separate age-adjusted model. In our final multivariate model, we adjusted for age, modified BMI, walking for exercise (yes/no), alcohol consumption, cigarette smoking, education, parity, age at first birth, family history of breast cancer, history of benign breast disease, age at menarche, and age at menopause. Risk estimates for the association between hip and spine BMD and breast cancer were limited to cases diagnosed after the second examination (1988-1990) (n=65).

Table 1.—Selection of Subjects

	No. (%)
Total original cohort	9704 (100)
Exclusions	1689 (17.4)
Prevalent breast cancer reported at year 1	506 (5.2)
Died prior to follow-up	365 (3.7)
No breast cancer information at year 1	160 (1.6)
No breast cancer information at follow-up	618 (6.3)
Breast cancer not confirmed*	40 (0.4)
Eligible for analysis	8015 (83)
Total cases	121 (1.2)
Total controls	7894 (81.3)
Exclude ERT† users	
Cases	97 (1.0)
Controls	6757 (69.6)
Total cohort in this analysis	6854 (70.6)

*Breast cancer not confirmed by medical records or denied breast cancer on interview (n=24), refused interview (n=7), or unavailable for follow-up (n=9).

†ERT indicates estrogen replacement therapy.

RESULTS

The average incidence of breast cancer in our cohort was 4.3 per 1000 person-years. There was little difference in the mean age or education of the breast cancer cases compared with controls (Table 2). The mean BMD was significantly higher among breast cancer cases than controls at all BMD sites. The mean body weight and BMI tended to be higher among the cases. There were no differences between cases and controls for waist to hip ratio, height at age 25 years, history of surgical menopause, age at menopause, age at menarche, nulliparity, number of live births, physical activity, smoking, or use of calcium supplements. Alcohol consumption was slightly higher among the cases compared with the controls. The proportion of breast cancer cases (17%) reporting a family history of breast cancer was similar to that of the controls (14.7%). There was no significant difference between cases and controls in the proportion of women with a history of benign breast disease, history of osteoporosis, or past use of estrogen (Table 2).

Increased BMD was independently associated with an increased risk of subsequent breast cancer (Table 3). The RR of breast cancer increased by 30% to

50% for each SD increase in BMD. The increased risk of breast cancer was observed for all BMD sites. Exclusion of cases with carcinoma in situ had little effect on the results. Additional adjustment for the degree of obesity or family history of breast cancer resulted in little change in the RR estimates. In our final multivariate model, we adjusted for many factors that have been related to both BMD and breast cancer, and results were similar (Table 3).

There was a direct relationship between age-adjusted BMD and risk of breast cancer (Table 4). The age-adjusted incidence rate of breast cancer was lowest among those with low BMD. Women with the highest BMD were at 2.0 to 2.5 times increased risk of breast cancer compared with those with the lowest BMD. A test for linear trend was statistically significant for all BMD sites ($P<.05$).

COMMENT

We have demonstrated that increased BMD of the radius, hip, or spine is significantly associated with an increased risk of subsequent breast cancer. The magnitude of the RR was strong with more than a 2-fold greater risk among the women with the highest BMD. Indeed, the association between BMD and breast cancer was similar in magnitude—though opposite in direction—to the association between BMD and all fractures.[30]

The association between BMD and breast cancer could be confounded by use of exogenous estrogen. However, we excluded all women reporting current use of estrogen at baseline, and there were no differences in the proportion of women who reported past use of estrogen among cases and controls. Exclusion of the small number of carcinoma in situ cases revealed similar results.

The association between BMD and breast cancer was similar in magnitude to the risk observed for other strong predictors of breast cancer (mother or sister with history of breast cancer; radiation to the chest in moderate to high doses), but was much stronger than that observed for other risk factors such as socioeconomic status, age at first full-term pregnancy, age at menarche, or obesity.[31]

The observation that BMD predicts breast cancer suggests a linkage between 2 of the most common conditions affecting a woman's health. One third to one half of older US women have low BMD in the hip,[32] and the lifetime risk of vertebral fracture in women is about 33%.[33] Twelve percent of women will have breast cancer diagnosed in their lifetime.[34] Both of these diseases have serious consequences. Identification of the common denominator for these 2 conditions will have major implications for studying the etiology and prevention of both conditions.

Our findings suggest that the risk of

Table 2.—Descriptive Characteristics of Subjects

Characteristic	Controls (n=6757)	Incident Breast Cancer Cases (n=97)	P
Age, y, mean±SD	71.5±5.2	70.9±0.09	.25
Education, y, mean±SD	12.5±2.8	12.8±3.1	.24
Bone mineral density, g/cm², mean±SD			
Radius			
Proximal	0.63±0.10	0.66±0.09	.003
Distal	0.36±0.08	0.38±0.08	.01
Calcaneus	0.40±0.09	0.42±0.08	.07
Total hip*	0.75±0.13	0.81±0.13	<.001
Lumbar spine*	0.84±0.16	0.90±0.15	.006
Body weight, kg, mean±SD	67.6±13.1	69.9±12.8	.09
BMI, kg/m², mean±SD†	25.6±4.6	26.5±5.2	.06
Waist/hip ratio, mean±SD	0.81±0.07	0.81±0.06	.57
Height at age 25 y, cm, mean±SD	162.5±5.9	162.5±6.2	.79
Age at menopause, y, mean±SD	47.1±6.3	46.7±5.5	.50
Age at menarche, y, mean±SD	13.1±1.48	12.8±1.58	.08
Nulliparous, %	18.4	16.1	.57
Surgical menopause, %	9.3	11.7	.43
Live births, No., mean±SD‡	2.7±1.6	2.5±1.6	.19
Physical activity			
Expenditure, kJ/wk, mean±SD	6758±7014	7203±5993	.47
Blocks walked per d, mean±SD	12.2±10.3	12.0±9.3	.88
Walks for exercise, %	50.6	54.6	.43
Alcohol, drinks per wk, mean±SD	1.9±3.9	2.7±4.6	.08
Smoking, %			
Current	9.6	5.3	.19
Past	25.3	29.2	
Calcium supplement use, %			
Current	40	40	.69
Past	8	10	
Family history of breast cancer, %	14.7	17	.58
Benign breast disease, %	13.1	15.4	.52
History of osteoporosis, %	15.9	13.5	.53
Estrogen use, %			
Past	32.3	33.0	.89
Never	67.7	67.0	

*Among cases diagnosed after the second clinical examination, including spine and hip bone mineral density measurements (n=65).
†BMI indicates body mass index (baseline weight divided by the square of height at age 25 years).
‡Among parous women.

Table 3.—Relative Risk and 95% Confidence Interval of Breast Cancer by Bone Mineral Density (BMD)*

BMD Site (SD)	Age-Adjusted	Age-Adjusted, Excluding CIS†	Age- and BMI-Adjusted‡	Age- and Family History–Adjusted	Multivariate-Adjusted§
Proximal radius (0.10)	1.34 (1.09-1.62)	1.35 (1.10-1.66)	1.30 (1.05-1.62)	1.38 (1.11-1.71)	1.30 (1.02-1.67)
Distal radius (0.09)	1.37 (1.11-1.69)	1.31 (1.10-1.66)	1.33 (1.07-1.66)	1.39 (1.11-1.75)	1.50 (1.16-1.95)
Calcaneus (0.10)	1.20 (0.97-1.49)	1.21 (0.97-1.21)	1.14 (0.89-1.45)	1.16 (0.92-1.47)	1.15 (0.87-1.52)
Total hip‖ (0.13)	1.48 (1.17-1.88)	1.55 (1.22-1.98)	1.40 (1.07-1.83)	1.52 (1.18-1.97)	1.39 (1.01-1.90)
Total spine‖ (0.17)	1.37 (1.09-1.72)	1.39 (1.09-1.75)	1.28 (1.00-1.65)	1.44 (1.13-1.85)	1.28 (0.95-1.71)

*Relative risk estimated for BMD in terms of 1 SD increase in BMD (g/cm²).
†Excluding 4 cases of carcinoma in situ (CIS).
‡BMI indicates body mass index (baseline weight divided by the square of height at age 25 years).
§Adjusted for age, education, modified BMI, take walks for exercise, alcohol consumption, smoking, parity, age at first birth, age at menarche, age at menopause, family history of breast cancer, and history of benign breast disease.
‖Including only cases diagnosed after the second clinical examination, including spine and hip BMD (n=65) measurements.

breast cancer associated with hormone replacement therapy may have been underestimated by previous investigators because osteoporosis is a primary indication for its use.[35,36] In our cohort, the 4 major reasons for initiating estrogen therapy were "hysterectomy," "menopausal symptoms," "prescribed by my doctor," and "to prevent or treat osteoporosis."[35] However, history of osteoporosis was a major determinant of continued long-term use of estrogen.[36] Assuming that BMD reflects endogenous estrogen levels, women with osteoporosis would have had relatively low endogenous estrogen levels, and so the addition of estrogen may not increase the risk of breast cancer. However, if women with normal BMD and normal or high endogenous estrogen were to take exogenous estrogen for other indications (eg, to prevent cardiovascular disease), it is possible that the combination of high endogenous plus exogenous estrogens could increase the risk of breast cancer. This hypothesis has not been tested. Clinical trials that include measurement of BMD are needed to reevaluate the balance of risks and benefits of hormone replacement therapy with regard to breast cancer, osteoporotic fractures, and coronary heart disease.

Our results are consistent with the hypothesis that long-term exposure to estrogen in women as measured by BMD is an important risk factor for breast cancer. It is possible, however, that the observed association between BMD and breast cancer reflects other hormonal factors besides estrogen.[37,38] For example, insulin levels have been shown to be directly related to BMD[39] and may also be related to the risk of breast cancer, possibly by interacting with the type I insulin-like growth factor receptor.[40] Insulin-like growth factors stimulate cell division in bone[37] and are potent mitogens in breast cancer tissue culture.[41] Complex feedback mechanisms may be involved among growth hormone, insulin-like growth factors, and estrogen, as well as other hormones.[37,38]

Our findings are consistent with the observation that women with endometrial cancer, a condition characterized by estrogen excess, have a reduced risk of fracture.[42] In addition, a 12-year follow-up study of women with distal forearm fractures reported significantly fewer breast cancer cases than expected.[43] Similarly, Persson et al[44] found a significantly reduced incidence of breast cancer after the occurrence of a first hip fracture.[44] Other studies, however, found no significant reduction in fracture risk among women with breast cancer.[45,46] Only 1 study directly measured BMD in breast cancer cases and controls. No difference in radial BMD between groups was found,[47] perhaps because BMD was measured after the diagnosis of breast cancer and could have been influenced by the disease itself or its treatment.

Table 4.—Age-Adjusted Incidence and Relative Risk (RR) and 95% Confidence Interval (CI) of Breast Cancer by Quartile of Bone Mineral Density, Excluding Current Estrogen Users

Measurement Site (g/cm²)	No.	Incidence Rate per 1000 Person-Years	RR (95% CI)	*P* (Trend)
Proximal radius				
Quartile 1 (<0.56)	13	2.33	1.00 Referent	
Quartile 2 (0.56-0.64)	26	4.65	1.91 (0.98-3.73)	.01
Quartile 3 (0.65-0.71)	32	5.50	2.44 (1.27-4.70)	
Quartile 4 (>0.71)	26	5.13	2.29 (1.16-4.54)	
Distal radius				
Quartile 1 (<0.30)	14	2.46	1.00 Referent	
Quartile 2 (0.30-0.36)	26	4.23	1.91 (1.00-3.67)	.004
Quartile 3 (0.37-0.42)	27	4.68	2.06 (1.07-3.94)	
Quartile 4 (>0.42)	29	5.99	2.66 (1.39-5.07)	
Calcaneus				
Quartile 1 (<0.34)	12	2.12	1.00 Referent	
Quartile 2 (0.34-0.40)	27	4.50	2.13 (1.07-4.21)	.01
Quartile 3 (0.41-0.47)	29	5.10	2.41 (1.22-4.77)	
Quartile 4 (>0.47)	29	5.33	2.53 (1.27-5.02)	
Hip				
Quartile 1 (<0.66)	6	1.18	1.00 Referent	
Quartile 2 (0.66-0.75)	13	2.43	2.12 (0.80-5.59)	.001
Quartile 3 (0.76-0.83)	24	4.77	4.08 (1.65-10.05)	
Quartile 4 (0.84-1.47)	22	4.64	3.97 (1.58-9.70)	
Spine				
Quartile 1 (<0.41-0.73)	9	1.68	1.00 Referent	
Quartile 2 (0.74-0.84)	17	3.06	1.83 (0.81-4.10)	.01
Quartile 3 (0.85-0.96)	13	2.63	1.51 (0.65-3.54)	
Quartile 4 (0.97-1.84)	26	5.75	3.33 (1.56-7.12)	

There are several limitations to our study. Participants in the Study of Osteoporotic Fractures are not a representative sample of older women; they are volunteers who are somewhat healthier than those who did not participate. However, the age-adjusted incidence rate of breast cancer among our cohort was 4.3 per 1000 person-years, which is comparable with the incidence rate observed for white women aged 65 years and older in the United States (4.6 per 1000).[48] Some women may have had undiagnosed breast cancer on enrollment in our study. Because breast cancer may reduce BMD either directly through a parathyroid hormone–related protein[49] or indirectly through weight loss, we may have underestimated their "true" baseline BMD. Thus, the association between BMD and breast cancer that we observed may actually underestimate the association between BMD and risk of breast cancer. It is also possible that some women who developed breast cancer during our study may have died of other causes during follow-up before we were able to ascertain their breast cancer status. Because women with lower BMD have an increased risk of death,[50] we would have underestimated the risk of breast cancer among women with low BMD. However, the relationship between BMD and total mortality is too weak to explain the observed association between BMD and breast cancer.

Many of the cases of breast cancer are likely to have been identified following a screening mammography, making it possible that utilization rates of mammography differ across BMD and could contribute to the observed variation in breast cancer. We asked women about the use of mammography from entry into the study. The history of mammography over 4 years varied from about 73% for women in the lowest quartile of BMD to 78% among women with highest BMD. However, we analyzed the relationship between BMD and breast cancer separately among women who reported a mammogram, and the results were similar.

In summary, our prospective study is the first to report an association between BMD and subsequent breast cancer, linking 2 of the most common and important conditions affecting a woman's health. Identifying a common denominator for these conditions should substantially improve our understanding of their etiology and prevention. Our findings suggest that before estrogen replacement therapy becomes widely used for indications other than osteoporosis, that the balance of risks and benefits of hormone

replacement therapy should be reevaluated with respect to BMD, osteoporosis, breast cancer, and coronary heart disease. These findings have implications for the use and interpretation of bone densitometry and the balance of risks and benefits of hormone replacement therapy.

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This work was supported in part by Public Health Service research grants AR35582, AG05407, AG05394, AM35584, AR35582, and T32AG00181 from the National Institutes of Health.

The authors wish to acknowledge Amy Horner for her technical expertise in preparing the manuscript.

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Appendix B

SOF ID No. ______________

Name Code: ______________

Date: ______________

Study of Osteoporotic Fractures

Breast Cancer Questionnaire

VERSION 1.3

November 5, 1996

Breast cancer identified at:

- ☐ Visit 4
- ☐ Visit 5
- ☐ Visit 6

Information obtained from:

- ☐ participant
- ☐ next of kin
- ☐ contact
- ☐ medical
- ☐ other ______________

1 Has a doctor EVER told you that you had breast cancer?

☐ 1 YES ☐ 0 NO → IF NO, then do not complete this form.

A. If YES, when were you diagnosed with breast cancer: ____/____/____
Month Day Year

FOR CLINIC USE ONLY:

Visit #3 Date: ____/____/____
Month Day Year

1.) Was this breast cancer after Visit 3?

☐ 1 YES → IF YES, then complete form.
☐ 0 NO → IF NO, then do not complete form.

2.) Is this information already being collected for a Visit 4 or Visit 5 breast cancer?

☐ 1 YES → IF YES, then do not complete form.
☐ 0 NO → IF NO, then complete form.

B. What was the doctor's name and address?

Doctor's Name ________________________________

Address ________________________________

City ________________ State ________ Zip ________

C. **Were you in a hospital or clinic for this breast cancer?**

☐ 1 YES ☐ 0 NO → **If NO, Skip to Question 2 on page 4.**

D.1. **For each diagnosis of breast cancer, please record the name, address and date of each hospitalization or clinic visit.**

Date of Admission: ____/____/____ (Month Day Year) Date of Discharge: ____/____/____ (Month Day Year)

Hospital or Clinic Name ____________________

Address ____________________

City ____________ State ______ Zip ______

D.2. **For each diagnosis of breast cancer, please record the name, address and date of each hospitalization or clinic visit.**

Date of Admission: ____/____/____ (Month Day Year) Date of Discharge: ____/____/____ (Month Day Year)

Hospital or Clinic Name ____________________

Address ____________________

City ____________ State ______ Zip ______

D.3. **For each diagnosis of breast cancer, please record the name, address and date of each hospitalization or clinic visit.**

Date of Admission: ____/____/____ (Month Day Year) Date of Discharge: ____/____/____ (Month Day Year)

Hospital or Clinic Name ____________________

Address ____________________

City ____________ State ______ Zip ______

D.4. For each diagnosis of breast cancer, please record the name, address and date of each hospitalization or clinic visit. (Use another sheet of paper to list additional admissions.)

Date of Admission: ____/____/____ (Month Day Year) Date of Discharge: ____/____/____ (Month Day Year)

Hospital or Clinic Name ____________

Address ____________

City ____________ State ______ Zip ______

2 Did you have a biopsy for your breast cancer?

☐ 1 YES

☐ 0 NO

☐ 9 DON'T KNOW

→ **If NO or DON'T KNOW, Skip to Question 3 on page 5.**

A. Please record the biopsy date and the name and address of the hospital, clinic or doctor's office.

Date of Biopsy: ____/____/____ (Month Day Year)

Doctor's Name ____________

Hospital, Clinic or Doctor's Office Name ____________

Address ____________

City ____________ State ______ Zip ______

3 **How was your breast cancer first discovered?**

Self-examination	☐ 1 YES	☐ 0 NO	☐ 9 DON'T KNOW
Routine examination by physician	☐ 1 YES	☐ 0 NO	☐ 9 DON'T KNOW
Mammogram	☐ 1 YES	☐ 0 NO	☐ 9 DON'T KNOW

Other (please list)____

____

____

Complete this form for all newly-diagnosed breast cancers.

COMMENTS	-Affix label here- SOF ID:__________ First Name__________ Last Name__________
To be completed by Local Physician Adjudicator: Date Completed: ____/____/____ (Month Day Year) Physician Adjudicator:__________	*To be completed by Outcomes Specialist:* Staff Person:__________

Items 1 through 4 to be completed by Outcomes Specialist.

ICD-9-CM Discharge Diagnosis Codes:

1. Record all ICD-9-CM diagnosis codes pertinent to breast cancer in the order they are listed on the hospital face sheet or physician attestation sheet. If there are more diagnosis codes than space available, record on a separate page and append to this form. (Do not report codes with an E or V prefix.)

1. _ _ _ . _ _	5. _ _ _ . _ _	9. _ _ _ . _ _	13. _ _ _ . _ _
2. _ _ _ . _ _	6. _ _ _ . _ _	10. _ _ _ . _ _	14. _ _ _ . _ _
3. _ _ _ . _ _	7. _ _ _ . _ _	11. _ _ _ . _ _	15. _ _ _ . _ _
4. _ _ _ . _ _	8. _ _ _ . _ _	12. _ _ _ . _ _	16. _ _ _ . _ _

ICD-9-CM Procedure Codes:

2. Record all ICD-9-CM procedure codes pertinent to breast cancer in the order they are listed on the hospital face sheet or physician attestation sheet. If there are more procedure codes than space available, record on a separate page and append to this form.

1. _ _ _ . _ _	5. _ _ _ . _ _	9. _ _ _ . _ _	13. _ _ _ . _ _
2. _ _ _ . _ _	6. _ _ _ . _ _	10. _ _ _ . _ _	14. _ _ _ . _ _
3. _ _ _ . _ _	7. _ _ _ . _ _	11. _ _ _ . _ _	15. _ _ _ . _ _
4. _ _ _ . _ _	8. _ _ _ . _ _	12. _ _ _ . _ _	16. _ _ _ . _ _

Discharge Diagnoses:

3. Please record all discharge diagnoses pertinent to breast cancer in the order they are listed on the hospital face sheet or discharge summary. If there are more diagnoses than space available, record on a separate page and append to this form.

3.1. Discharge diagnoses recorded below? ☐0 No ☐1 Yes

1.__________	9.__________
2.__________	10.__________
3.__________	11.__________
4.__________	12.__________
5.__________	13.__________
6.__________	14.__________
7.__________	15.__________
8.__________	16.__________

Procedures:

4. Please record all procedures pertinent to breast cancer in the order they are listed on the hospital face sheet or other sources. If there are more procedures than space available, record on a separate page and append to this form.

4.1. Procedures recorded below? ☐0 No ☐1 Yes

1.__________	9.__________
2.__________	10.__________
3.__________	11.__________
4.__________	12.__________
5.__________	13.__________
6.__________	14.__________
7.__________	15.__________
8.__________	16.__________

Item 5 to be completed by Physician Adjudicator:

5. Was breast cancer diagnosed?

☐ No
☐ Yes ⟶ IF YES, *then complete questions 6-11.*

6. Date of diagnosis: ____/____/____
Month Day Year

7. Tumor Behavior:

   ☐1 Lobular In-Situ.

   ☐2 Ductal In-Situ.

   ☐3 Invasive Breast Cancer, Localized to Breast.

   ☐4 Invasive Breast Cancer with Regional Lymph Nodes.

   ☐5 Advanced Breast Cancer, Evidence of Metastasis beyond Breast and Axillary Nodes.

   ☐6 Other, specify________________________________

8. Diagnostic Confirmation Status: (***Mark one. If more than one category applies, mark the first applicable category.***)

   Microscopically Confirmed:

   ☐1 Positive histology (pathology)

   ☐2 Positive exfoliative cytology, no positive histology

   ☐3 Positive histology (pathology), distant metastatic site only

   ☐4 Positive microscopic confirmation, method not specified

   Not Microscopically Confirmed:

   ☐5 Positive laboratory test/marker study

   ☐6 Direct visualization without microscopic confirmation

   ☐7 Radiographic and other imaging techniques without microscopic confirmation

   ☐8 Clinical diagnosis only (other than 5, 6 or 7)

   Confirmation Unknown:

   ☐9 Unknown if microscopically confirmed

9. Staging of Tumor:

   TNM Stage:

   ☐0 In-Situ ☐1 I ☐2 IIN_0 ☐3 IIN_1 ☐4 III ☐5 IV ☐9 Unknown

10. Estrogen and Progesterone Receptor Assay Status:

    ERA: ☐1 Positive ☐2 Negative ☐3 Borderline ☐8 Ordered, not available ☐9 No information or unknown

    PRA: ☐1 Positive ☐2 Negative ☐3 Borderline ☐8 Ordered, not available ☐9 No information or unknown

____

Responsible Adjudicator Signature

INITIAL NOTIFICATION OF BREAST CANCER (BC1)

Complete as much as possible of this form and send a copy of this form to the Coordinating Center within 5 working days after learning of a possible breast cancer.

Participant's name: ______________________ **ID:** __________

Phone: ______________ **Name Code:** ______

Today's Date: ______________

Date Clinic Notified: __________ Date of Breast Cancer: __________

Name and address of informant if different than patient.

Name: ______________________

Address: ______________________

____

Phone: ______________________

Was the participant in a hospital or clinic for this breast cancer?

☐ No ☐ Yes

Name of hospital or clinic: ______________________

Address: ______________________

____

Phone: ______________________
(Area)

Name of person completing this form: ______________________

Date this form was completed: ______________ **Staff ID:** __________